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Comparative Activity and β-Lactamase Stability of Cefoperazone, a Piperazine Cephalosporin

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The in vitro activity and β-lactamase stability of 7-[D(−)-α-(4-ethyl-2,3-dioxopiperazino-carbonylamino)-*p*-hydroxyphenylacetamido]-3-[(1-methyl)-5-tetrazolylthiomethyl]-Δ^3-cephem-4-carboxylic acid (cefoperazone), a cephalosporin analog of piperacillin, were compared with the activities and stabilities of other cephalosporins and cephamycins. The compound was less active than cephalothin or cefamandole in inhibiting *Staphylococcus aureus*; it was as active as cefamandole and cefoxitin against most of the *Enterobacteriaceae* but less active than cefotaxime. It was more active than carbenicillin or piperacillin against *Pseudomonas aeruginosa*. In general, the compound was not active against *Bacteroides*. It was hydrolyzed by the β-lactamases of some *Escherichia coli* which hydrolyzed cefamandole, but was stable to most plasmid-mediated, chromosomally mediated, inducible β-lactamases in the *Enterobacteriaceae* and *Pseudomonas*.

Within the past few years a number of new cephalosporins with enlarged bacterial spectra have been developed. These cephalosporins have in vitro activity against β-lactamase-producing *Enterobacteriaceae*, *Haemophilus*, and *Neisseria* (3-7). At the same time there has been an increased appreciation of the frequency of infection due to several species of bacteria, as well as an enlightened awareness of the toxic potentials when several antibiotics are used simultaneously. This has prompted a search for antibiotics which are effective against the major organisms causing bacteremia in compromised patients. Although some newer cephalosporins, such as cefuroxime, cefamandole, and cefoxitin, inhibit β-lactamase-producing *Enterobacteriaceae*, they are ineffective against *Pseudomonas aeruginosa*. The development of 7-[D(−)-α-(4-ethyl-2,3-dioxopiperazino-carbonylamino)-*p*-hydroxyphenylacetamido]-3-[(1-methyl)-5-tetrazolylthiomethyl]-Δ^3-cephem-4-carboxylic acid, cefoperazone, a cephalosporin analog of piperacillin sodium, prompted us to evaluate its in vitro activity against bacterial isolates from hospitalized patients and to compare its activity with the activities of other new β-lactam agents, including cefotaxime (6).

MATERIALS AND METHODS

Samples of cefoperazone (Fig. 1) were obtained from Toyama, Lederle, and Pfizer. Cefotaxime was obtained from Hoechst-Roussel, and all other agents were gifts of their respective manufacturers.

Fresh dilutions of the compounds were prepared daily in either sterile medium or distilled water. Bacterial isolates were obtained from patients hospitalized at the Columbia Presbyterian Medical Center, New York, N.Y. In some experiments (when noted) isolates tested were known to be multiply resistant to antibiotics or to contain β-lactamases or both. Some isolates have been stored frozen for a number of years.

Susceptibility tests. Antimicrobial activity was measured by an agar dilution method with Mueller-Hinton (MH) agar unless specified otherwise. A final inoculum of 10^5 colony-forming units, prepared by dilution of a fresh overnight broth culture, was applied to agar by a replicating spot device. Broth dilutions were performed with 10^5 colony-forming units in tubes of 1 ml volume. Plates or tubes were incubated at 35°C for 18 h. The minimal inhibitory concentration (MIC) was defined as the lowest concentration of antibiotic that inhibited development of visible growth on agar or in broth. The minimal bactericidal concentration (MBC) was determined by plating 0.01-ml amounts from clear broth tubes onto blood agar plates. The MBC was the concentration at which there were fewer than five colonies after 24 h of incubation at 35°C. Susceptibility of streptococci was determined by using MH agar supplemented with 5% sheep blood. Susceptibility of *Neisseria* species and *Haemophilus* species was determined on chocolate MH agar with assays run in the presence of CO_2. Tube dilutions for these species were performed by using Levinthal broth. Anaerobic susceptibility was determined by using MH agar supplemented with sheep blood and vitamin K. Incubation of anaerobic cultures was for 48 h in GasPak jars (BBL Microbiology Systems).

Synergy study. Synergy of cefoperazone with other antibiotics was determined by the agar dilution technique previously described (1). Synergy was considered to be present when there was a fourfold decrease in the MICs of both agents.

β-Lactamase assays. Both the chromogenic sub-

strate nitrocefin (8) and a modified iodometric assay were used to determine the presence of β-lactamase in clinical isolates (5). Induction of β-lactamases was with cephalothin (25 μg/ml) present for 3 h (5). β-Lactamases were classified by a modification of a schema suggested by Sykes and Matthew (9). β-Lactamase activity with the partially purified or purified β-lactamases was determined by a spectrophotometric assay, using the change in absorbance at 255 nm with cephalosporins as substrates (7, 8).

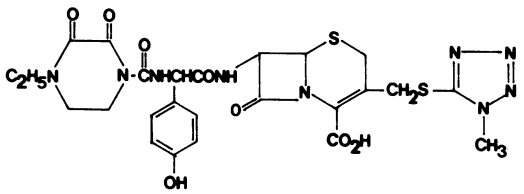

FIG. 1. *Structure of 7-[D(−)-α-(4-ethyl-2,3-dioxopiperazino-carbonylamino)-p-hydroxyphenylacetamido]-3-[(1-methyl)-5-tetrazolylthiomethyl]-Δ³-cephem-4-carboxylic acid, cefoperazone.*

Protein binding. Protein binding was determined by the agar well diffusion method; zones of inhibition of growth of test *Escherichia coli* 3989 (our collection) were compared, using cefoperazone which had been dissolved in phosphate buffer and pooled, heat-inactivated normal human serum (6).

RESULTS

The in vitro activity of cefoperazone was compared with the activities of other β-lactam antibiotics (Table 1). Cefoperazone was less active

TABLE 1. *Comparative activity of cefoperazone and other β-lactam antibiotics*

Organism (no. of strains)	Drug	MIC (μg/ml)		
		Range	For 50% of isolates	For 90% of isolates
S. aureus (16)	Cefoperazone	1.6–3.1	3.1	3.1
	Carbenicillin	0.8–12.5	12.5	12.5
	Cephalothin	0.05–0.4	0.1	0.2
	Cefoxitin	1.6–6.2	1.6	6.2
	Cefotaxime	0.4–3.1	1.6	3.1
	Piperacillin	0.4–50	12.5	25
S. epidermis (15)	Cefoperazone	0.8–50	3.1	3.1
	Carbenicillin	1.6–>100	12.5	25
	Cephalothin	0.2–25	0.4	1.6
	Cefoxitin	1.6–25	3.1	6.2
	Cefotaxime	0.4–12.5	6.2	12.5
S. pyogenes (12)	Cefoperazone	<0.1–1.6	0.2	1.6
	Carbenicillin	0.8–6.2	1.6	1.6
	Piperacillin	<0.1–1.6	0.4	0.4
	Cephalothin	0.05–0.2	0.05	0.1
	Cefotaxime	<0.1–0.2	<0.1	0.1
S. agalactiae (10)	Cefoperazone	0.2–3.1	0.4	0.8
	Ampicillin	0.05–0.2	0.1	0.2
	Cephalothin	0.2–6.2	0.8	1.6
	Cefamandole	0.1–3.1	0.4	1.6
S. faecalis (19)	Cefoperazone	0.4–50	25	50
	Carbenicillin	1.6–50	25	50
	Piperacillin	1.6–6.2	3.1	3.1
	Cephalothin	3.1–100	25	50
	Cefoxitin	25–>100	100	>100
	Cefotaxime	0.2–>100	12.5	100
H. influenzae (15)	Cefoperazone	0.2–0.8	0.4	0.8
	Ampicillin	0.05–>100	0.2	0.8
	Cefamandole	0.1–0.8	0.2	0.4
	Cefotaxime	0.05–0.8	0.1	0.8
H. parainfluenzae (7)	Cefoperazone	0.4–3.1	0.8	1.6
	Ampicillin	0.2–>100	0.4	1.6
	Piperacillin	0.2–>100	0.4	1.6
	Cefotaxime	0.5–0.8	0.2	0.8
N. gonorrhoeae (14)	Cefoperazone	0.2–1.6	0.1	0.2
	Ampicillin	0.1–>100	0.2	0.8
	Piperacillin	0.1–>100	0.4	1.6
	Cefoxitin	0.2–3.1	0.4	0.8
	Cefotaxime	0.01–0.1	0.05	0.1
Listeria monocytogenes (10)	Cefoperazone	6.3–50	25	50
	Ampicillin	0.2–1.6	0.8	1.6
	Cefotaxime	6.3–50	25	100

TABLE 2. *Comparative activity of cefoperazone, penicillins, and cephalosporins against enteric species*

Organism (no. of strains)	Drug	MIC (μg/ml)		
		Range	For 50% of isolates	For 90% of isolates
E. coli (78)	Cefoperazone	<0.1->100	0.8	25
	Carbenicillin	1.6->100	25	>100
	Piperacillin	0.4->100	12.5	>100
	Cefoxitin	1.6-12.5	3.1	6.2
	Cefamandole	0.2-100	0.8	12.5
	Cefotaxime	<0.1-3.1	<0.1	0.4
E. aerogenes (18)	Cefoperazone	<0.1-6.2	0.2	0.8
	Carbenicillin	3.1->200	6.2	100
	Piperacillin	0.8->200	3.1	50
	Cefamandole	1.6->100	3.1	50
	Cefotaxime	0.1->100	0.1	0.4
E. cloacae (18)	Cefoperazone	<0.1->100	0.4	100
	Carbenicillin	3.1->200	3.1	100
	Piperacillin	1.6->200	1.6	100
	Cefamandole	0.8->100	3.1	50
	Cefotaxime	<0.1-0.8	<0.1	0.4
K. pneumoniae (32)	Cefoperazone	0.1->100	1.6	50
	Cephalothin	1.6-100	6.2	50
	Cefamandole	0.4-100	3.1	50
	Piperacillin	0.8->200	25	100
	Cefoxitin	0.8->100	3.1	25
	Cefotaxime	<0.1-6.3	<0.1	0.4
P. mirabilis (31)	Cefoperazone	0.4-50	0.8	3.1
	Carbenicillin	0.2->200	0.8	1.6
	Piperacillin	0.2->200	0.4	1.6
	Cefoxitin	0.4-25	3.1	6.2
	Cefotaxime	<0.1-3.1	<0.1	0.1
P. morganii (15)	Cefoperazone	0.8-6.2	1.6	3.1
	Carbenicillin	0.8->200	0.2	12.5
	Cefoxitin	6.2->100	12.5	12.5
	Cefotaxime	0.1-1.6	0.1	1.6
P. rettgeri (11)	Cefoperazone	0.8-50	12.5	50
	Carbenicillin	<0.1->200	0.8	>200
	Piperacillin	<0.1->200	25	>200
	Cefoxitin	1.6->100	3.1	50
	Cefotaxime	<0.1-1.6	<0.1	1.6
P. vulgaris (4)	Cefoperazone	0.4-50	0.8	50
	Carbenicillin	3.1->200	3.1	100
	Piperacillin	0.1->100	0.4	100
	Cefoxitin	1.6-3.1	1.6	3.1
	Cefotaxime	0.1-1.25	0.1	12.5
Citrobacter (32)	Cefoperazone	0.1->100	0.4	12.5
	Carbenicillin	0.8->200	100	>200
	Piperacillin	0.4->200	6.2	100
	Cephalothin	0.8->100	25	>100
	Cefoxitin	0.8->100	12.5	100
	Cefotaxime	<0.1->100	<0.1	25
Acinetobacter (15)	Cefoperazone	0.8->100	100	>100
	Carbenicillin	0.8->200	25	100
	Piperacillin	1.6->100	12.5	100
	Cefamandole	3.1->100	100	>100
	Cefoxitin	1.6->100	100	>100
	Cefotaxime	<0.1->100	25	100
Providencia (16)	Cefoperazone	0.2-50	12.5	50
	Carbenicillin	0.4->200	100	>200
	Piperacillin	0.4->200	100	>200
	Cefamandole	1.6->100	6.2	12.5
	Cefotaxime	<0.1-3.1	0.4	1.6

TABLE 2. *Cont.*

Organism (no. of strains)	Drug	MIC (μg/ml)		
		Range	For 50% of isolates	For 90% of isolates
Serratia (32)	Cefoperazone	0.8->200	100	>100
	Carbenicillin	12.5->200	100	>200
	Piperacillin	50->100	100	>200
	Cefoxitin	25->100	100	>200
	Cefotaxime	0.2->100	50	>100
Salmonella (15)	Cefoperazone	0.4-50	0.8	50
	Carbenicillin	3.1->200	6.2	100
	Piperacillin	0.8->200	0.8	100
	Cefoxitin	1.6-6.2	1.6	3.1
	Cefotaxime	<0.1-0.2	<0.1	0.1
Shigella (16)	Cefoperazone	<0.1-25	0.4	100
	Carbenicillin	0.2->200	3.1	100
	Piperacillin	<0.1->200	0.4	100
	Cefoxitin	1.6-100	3.1	100
	Cefotaxime	<0.1-1.6	0.1	0.8
Bacteroides (23)	Cefoperazone	3.1->200	50	100
	Carbenicillin	12.5->200	50	100
	Piperacillin	3.1-100	6.2	50
	Cefoxitin	3.1-100	12.5	50
	Cefotaxime	3.1-100	25	100
Pseudomonas (64)	Cefoperazone	3.1->200	6.2	50
	Carbenicillin	3.1->200	50	100
	Piperacillin	3.1->200	6.2	100
	Mezlocillin	3.1->200	25	100
	Cefotaxime	0.4-100	25	100

against *Staphylococcus aureus* than cephalothin or cefamandole but was more active than piperacillin and comparable in activity to cefoxitin and cefotaxime. The activity of cefoperazone against *Staphylococcus epidermidis* was similar to its activity against *S. aureus*. Cefoperazone was less active against *Streptococcus pyogenes* than cephalothin, piperacillin, carbenicillin, or cefotaxime, with an MIC of 1.6 μg/ml required to inhibit 90% of the isolates. *Streptococcus agalactiae* group B isolates were inhibited in a similar manner. Cefoperazone did not inhibit *Streptococcus faecalis* as did piperacillin, and the compound showed the similar poor activity that all of the cephalosporins have against true enterococci. Cefoperazone showed poor inhibitory activity against *Listeria*, as did cefotaxime.

Cefoperazone inhibited *Haemophilus influenzae* and *H. parainfluenzae* as well as piperacillin and cefoxitin did, but less well than cefotaxime. It inhibited the three β-lactamase-producing *H. influenzae* isolates tested as well as cefoxitin, cefamandole, and cefotaxime did. The activity of cefoperazone against *Neisseria meningitidis* and *N. gonorrhoeae* was equivalent to that of the newer cephalosporins, and cefoperazone inhibited β-lactamase-producing *N. gonorrhoeae* (three isolates tested) at concentrations comparable to those at which cefoxitin and cefotaxime inhibited these organisms.

Cefoperazone inhibited the majority of *E. coli* at concentrations below 3.1 μg/ml. The majority (90%) of out-patient isolates of *E. coli* were inhibited by 0.8 μg/ml or less, but there was a distinct population of *E. coli*, usually strains from nosocomial infections, which were resistant to cefoperazone but were inhibited by cefotaxime and cefoxitin. Cefoperazone had activity similar to that of cefoxitin and cefamandole against *Klebsiella pneumoniae*, but was less active than cefotaxime (Table 2). It inhibited *Enterobacter aerogenes*, *E. cloacae*, and *E. hafnia* (data not shown) more effectively than did any of the other agents tested, with the exception of cefotaxime. Some *E. cloacae*, however, were not inhibited by 100 μg/ml. Although less active than cefotaxime, cefoperazone inhibited *Proteus mirabilis* as effectively as carbenicillin and piperacillin and better than cefoxitin and cephalothin. The activity of cefoperazone against the indole-positive *Proteus*, *P. morganii*, *P. rettgeri*, and *P. vulgaris* was similar to the activities of carbenicillin, piperacillin, and cefoxitin and slightly less than that of cefotaxime. Cefoperazone was less active than carbenicillin against *Providencia* and less active than cefoxitin and

cefotaxime, which inhibited carbenicillin-resistant *Providencia*.

Cefoperazone was more active than carbenicillin, piperacillin, cephalothin, and cefoxitin against *Salmonella* and *Shigella*, but it was severalfold less active than cefotaxime. Cefoperazone inhibited the majority of *Citrobacter* at concentrations below 3 μg/ml but was a more active agent than carbenicillin, piperacillin, or cefoxitin and had an activity equal to that of cefotaxime. The compound inhibited *Serratia marcescens* susceptible to carbenicillin at concentrations of 12.5 μg/ml or less, but it failed to inhibit the more resistant isolates and did not inhibit isolates resistant to cefoxitin and cefotaxime. It was less active than piperacillin or carbenicillin against *Acinetobacter* and had activity comparable to that of cefoxitin.

Cefoperazone showed poor activity against *Bacteroides*, including *B. fragilis* isolates, and many were resistant to the agent. It had less activity than carbenicillin, piperacillin, or cefoxitin.

Cefoperazone did inhibit other anaerobic organisms, such as *Bifidobacterium* (two isolates tested), *Clostridium* (two tested), and *Fusobacterium* (two tested) at concentrations of 3.1 μg/ml or less. The MICs against three peptostreptococci, however, were 100 μg/ml.

Cefoperazone inhibited *P. aeruginosa* at lower concentrations than did any of the other agents tested. At 25 μg/ml, 80% of *P. aeruginosa* isolates were inhibited by cefoperazone, whereas 16, 70, 0 and 64% were inhibited by carbenicillin, piperacillin, cefoxitin, and cefotaxime, respectively.

The effect of the type of growth medium upon the activity of cefoperazone was studied by using broth and agar, nutrient broth, brain heart infusion broth, and Trypticase soy broth. There were no major differences in MICs against the 24 isolates of *S. aureus*, *E. coli*, *K. pneumoniae*, *E. cloacae*, *P. morganii*, *Citrobacter fruendii*, and *P. aeruginosa*. Cefoperazone was not stable in neutral buffer at 37°C. It lost 41% of its potency in 60 min and 87% in 3 h.

There were differences between the MICs and MBCs for organisms in each of the five species tested. The MBCs were identical or only 2-fold greater than the MICs for 44% of the isolates and 8- or 16-fold greater for 47% of the isolates. A greater difference between MICs and MBCs was seen for *Klebsiella* than for *Enterobacter*.

There was a marked effect of the inoculum size on the MIC. All of the *E. coli* (10 isolates tested), *K. pneumoniae* (10 tested), *Enterobacter* (10 tested), indole-positive *Proteus* (10 tested), and *P. aeruginosa* (10 tested) had MICs and MBCs of 100 μg/ml or greater with inocula of 10^7 colony-forming units, compared with MICs of 0.4 to 50 μg/ml with inocula of 10^5 colony-forming units.

Table 3 shows the activity of cefoperazone against isolates resistant to selected β-lactam antibiotics. Of the ampicillin-resistant *E. coli*, 42% were resistant to cefoperazone, and the *E. coli* isolates resistant to cefazolin and cefamandole were resistant to cefoperazone. Many of the *Klebsiella* resistant to the other agents were also resistant to cefoperazone. In contrast, most *Enterobacter* and *Citrobacter* resistant to carbenicillin, piperacillin, or cefamandole were inhibited by cefoperazone. More than half the *Providencia*, *P. morganii*, *P. rettgeri*, *P. vulgaris*, and *P. mirabilis* isolates resistant to carbenicillin, piperacillin, or cefoxitin were inhibited by cefoperazone. Only a few isolates of *Serratia* resistant to piperacillin were inhibited by cefoperazone; but cefoperazone inhibited 70% of *P. aeruginosa* isolates resistant to carbenicillin, 71% resistant to piperacillin, and three of four isolates resistant to cefotaxime.

Direct comparisons of the MICs for β-lactamase-producing isolates are given in Table 4. Cefoperazone failed to inhibit a number of organisms which were inhibited by other β-lactamase-stable cephalosporins, such as cefoxitin and cefuroxime. In all cases it was less active than cefotaxime.

Comparisons of the activity of cefoperazone against isolates which contained β-lactamases versus its activity against those isolates that lacked this enzyme are given in Table 5. The MICs of cefoperazone were consistently higher for β-lactamase-containing isolates than were the MICs for strains in which β-lactamases could not be demonstrated as either constitutive enzymes or inducible enzymes. However, Fig. 2 illustrates that the MICs ranged from 0.2 to >100 μg/ml for isolates whether or not a β-lactamase could be demonstrated. If only the *Enterobacteriaceae* were considered, the organisms which contained high concentrations of a constitutive β-lactamase which was either primarily of a penicillinase type (*E. coli* or *Salmonella typhimurium*) or cephalosporinase type (*Klebsiella* or *P. rettgeri*) had MICs of 100 μg/ml or greater. The organisms which contained inducible β-lactamases of primary cephalosporin activity (*P. morganii*, *P. rettgeri*, *E. aerogenes*, and *E. cloacae*) were inhibited by 6.2 μg or less of cefoperazone per ml.

Compared with cephaloridine and cephalothin, cefoperazone was resistant to hydrolysis by a number of β-lactamases of plasmid and chromosomal origin (Table 6). However, it was hy-

TABLE 3. *Activity of cefoperazone against isolates resistant to other β-lactam antibiotics*

Organism	Resistant to:[a]	No. of strains tested	No. susceptible to cefoperazone[b]	No. resistant to cefoperazone
E. coli	Ampicillin	38	20	18
	Piperacillin	15	9	6
	Cefazolin	3		3
	Cefamandole	1		1
K. pneumoniae	Cephalothin	6	4	2
	Cefazolin	8	2	6
	Cefoxitin	2	2	
	Piperacillin	15	6	9
Enterobacter	Carbenicillin	10	8	2
	Piperacillin	6	4	2
	Cefamandole	6	4	2
Citrobacter	Carbenicillin	14	12	2
	Piperacillin	7	5	2
	Cefamandole	3	3	
Proteus, Providencia	Carbenicillin	18	7	11
	Piperacillin	18	5	13
	Cefoxitin	3	1	2
Serratia	Carbenicillin	29	4	25
	Piperacillin	29	4	25
	Cefoxitin	21	1	20
Pseudomonas	Carbenicillin	23[c]	16[d]	7
	Piperacillin	7[c]	5[d]	2
	Cefotaxime	4[c]	3[d]	1

[a] Isolates which were inhibited by ≥25 μg/ml of the agents per ml.
[b] Isolates which were inhibited by <25 μg/ml.
[c] Isolates which were inhibited by >50 μg/ml.
[d] Isolates which were inhibited by ≤50 μg/ml.

TABLE 4. *Comparative activity of major cephalosporins against cephalothin-carbenicillin-resistant isolates*

Organism	MIC (μg/ml) of:						
	Cefoperazone	Cephalothin	Cefamandole	Cefuroxime	Cefoxitin	Cefotaxime	Carbenicillin
E. coli	12.5	25	3.1	3.1	3.1	0.05	>400
E. coli	100	50	100	3.1	1.6	0.05	>400
K. pneumoniae	100	100	100	3.1	3.1	0.05	>400
K. pneumoniae	>100	50	50	1.6	1.6	0.05	>400
E. cloacae	>100	>400	>400	>400	>400	0.1	>400
P. mirabilis	>100	100	100	25	50	3.1	>400
C. freundii	0.4	>200	12.5	1.6	100	0.2	>400
S. marcescens	>100	>400	>400	>400	>400	25	>400
S. marcescens	1.6	>400	>400	>400	100	6.3	>400
P. rettgeri	>100	>400	>400	100	100	1.6	>400
Providencia stuarti	50	>400	200	200	25	0.8	>400
B. fragilis	50	>400	>200	>200	6.2	50	100

drolyzed by some *E. coli* β-lactamases. These *E. coli* also destroyed cefamandole.

To ascertain the synergistic potential of cefoperazone, it was combined with gentamicin and tested against *P. aeruginosa*. Figure 3, which is a plot of cefoperazone plus gentamicin at one-fourth the gentamicin MICs, shows that the combination of two agents was for the most part indifferent, although one-third of the isolates were synergistically inhibited.

The protein binding of cefoperazone was approximately 70% when determined by agar diffusion.

DISCUSSION

Cefoperazone is a new semisynthetic piperazine cephalosporin which combines many of the properties of piperacillin and the new cephalosporins, such as cefamandole. It was less active than cephalothin or cefamandole against *S. aureus* and less active than piperacillin against enterococci. It was more active than most of the

TABLE 5. *Range of MICs for β-lactamase-positive and -negative isolates*

Species (no. of isolates tested)[a]		MIC range (μg/ml) for: β-Lactamase-negative isolates	β-Lactamase-positive isolates
S. aureus	(10)	3.1–6.2	3.1–50
S. epidermidis	(10)	1.6–6.2	6.2
E. coli	(20)	0.05–3.1	0.8–>200
Enterobacter	(20)	0.4–3.1	0.8–>100
K. pneumoniae	(10)	0.2–3.1	6.2–>100
P. morganii	(5)	1.6–25	1.6–3.1
P. vulgaris	(5)	1.6	0.8–>100
P. rettgeri	(5)	1.6–6.2	6.2–>100
P. aeruginosa	(10)	12.5–100	25–50
Shigella sonnei	(10)	0.05–6.3	0.4–50
Salmonella	(10)	0.8–1.6	6.3–>100
P. mirabilis	(5)	0.8–1.6	>100
C. freundii	(10)	0.1	12.5–100
Citrobacter diversus	(10)	0.1–1.6	
Providencia	(10)	12.5–25	50–>100
Acinetobacter	(10)	1.6–25	>100

[a] The number of isolates containing and lacking β-lactamase was determined by assay with nitrocefin.

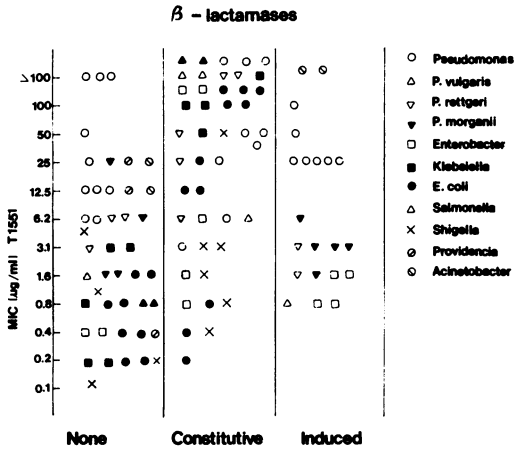

FIG. 2. *Correlation of MICs and presence of β-lactamases. T 1551, cefoperazone.*

other cephalosporins except cefotaxime against *E. coli*, but it failed to inhibit some ampicillin cefamandole-resistant *E. coli*. This appears to be due to hydrolysis by certain β-lactamases. The presence of constitutive plasmid-mediated β-lactamases in *E. coli*, *Salmonella*, and *Shigella* correlated with higher MICs.

The compound was resistant to most of the induced β-lactamases, which act primarily as cephalosporinases, and this resistance to hydrolysis correlated with its activity against many *P. morganii*, *E. cloacae*, *E. aerogenes*, and *P. aeruginosa*.

In general, cefoperazone seems to combine the properties of cefamandole and piperacillin, although it is less active than piperacillin against *S. faecalis*, *Acinetobacter*, and *Bacteroides* and less active than cefamandole against *S. aureus* and *S. pyogenes* (2, 3).

The effect of inoculum size, which has been

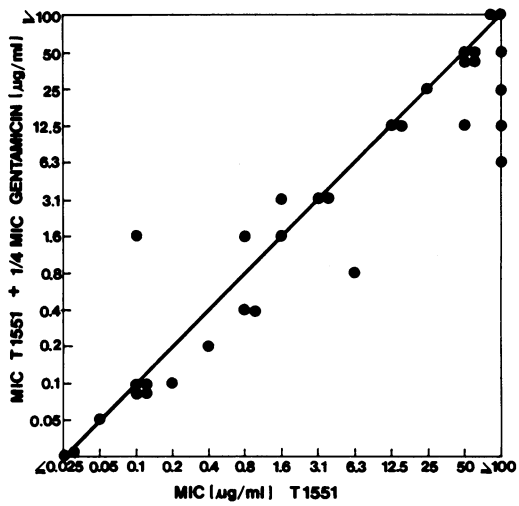

FIG. 3. *Comparative activity of cefoperazone (T 1551) alone and in combination with one-fourth the MIC of gentamicin against Enterobacteriaceae and Pseudomonas.*

TABLE 6. *Relative hydrolysis of cefoperazone by β-lactamases*

β-Lactamase type[a]	Source	Relative hydrolysis of: Cephaloridine	Cephalothin	Cefoxitin	Cefoperazone
Pl, Pen, Con	*P. aeruginosa*	100	25	0	0
Pl, PC, Oxa, Con	*Shigella sonnei*	100	23	0	0
Ch, Ceph, Ind	*C. freundii*	100	98	0	0
Ch, Ceph, Con	*P. morganii*	100	227	0	10
Ch, Pen, Ceph, Con	*K. pneumoniae*	100	63	0	7
Ch, Ceph, Ind	*P. aeruginosa*	100	163	0	5
Pl, Pen, Ind	*S. aureus*	100	5	0	0
Ch, PC, Con	*P. mirabilis*	100	155	0	8
Ceph, Pen, Con	*E. coli*	100	120	0	150

[a] Abbreviations: Pl, plasmid; Ch, chromosomal; Pen, primary substrate penicillins; Ceph, primary substrate cephalosporins; PC, either penicillins or cephalosporins hydrolyzed; Oxa, oxacillin hydrolyzed; Con, constitutive; Ind, induced.

reported for both piperacillin and cefamandole against selected species, also was seen with cefoperazone (2, 3). Some of this may be due to the 20 to 30% breakdown of the compound at pH 7.4 after 24 h. In general, the inhibitory and bactericidal concentrations were the same against *Enterobacteriaceae* but not against *P. aeruginosa*.

The enlarged spectrum of activity of this agent makes it an agent which deserves further evaluation in animal experiments and in the treatment of human infections. It undoubtedly should be compared with cefamandole, cefoxitin, and cefotaxime to establish its position in comparison with these other extended spectrum agents which already have shown great promise in the treatment of serious infections.

LITERATURE CITED

1. **Fu, K. P., and H. C. Neu.** 1978. A comparative study of the activity of cefamandole and other cephalosporins and analysis of the β-lactamase stability and synergy of cefamandole with aminoglycosides. J. Infect. Dis. **137**(Suppl):38–48.
2. **Fu, K. P., and H. C. Neu.** 1978. Piperacillin, a new penicillin active against many bacteria resistant to other penicillins. Antimicrob. Agents Chemother. **13**:358–367.
3. **Neu, H. C.** 1974. Cefamandole, a cephalosporin antibiotic with an unusually wide spectrum of activity. Antimicrob. Agents Chemother. **6**:177–182.
4. **Neu, H. C.** 1974. Cefoxitin, a semisynthetic cephamycin antibiotic: antibacterial spectrum and resistance to hydrolysis by gram-negative beta-lactamases. Antimicrob. Agents Chemother. **6**:170–176.
5. **Neu, H. C.** 1975. The role of β-lactamase in the resistance of gram-negative bacteria to penicillin and cephalosporin derivatives. Infect. Dis. Rev. **3**:130–149.
6. **Neu, H. C., N. Aswapokee, P. Aswapokee, and K. P. Fu.** 1979. HR 756, a new cephalosporin active against gram-positive and gram-negative aerobic and anaerobic bacteria. Antimicrob. Agents Chemother. **15**:273–281.
7. **Neu, H. C., and K. P. Fu.** 1978. Cefuroxime, a beta-lactamase-resistant cephalosporin with a broad spectrum of gram-positive and -negative activity. Antimicrob. Agents Chemother. **13**:657–664.
8. **O'Callaghan, C. H., A. Morris, S. M. Kirby and A. H. Shingler.** 1972. Novel method for detection of β-lactamases by using a chromogenic cephalosporin substrate. Antimicrob. Agents Chemother. **1**:283–288.
9. **Sykes, R. B., and M. Matthew.** 1976. The β-lactamases of gram-negative bacteria and their role in resistance to β-lactam antibiotics. J. Antimicrob. Chemother. **2**:115–157.